



Purepac Pharmaceutical Co.  
200 Elmora Avenue, Elizabeth, New Jersey 07207  
908-527-9100  
Fax: 908-527-0649

1274 '99 DEC -8 AID:15

December 6, 1999

Dockets Management Branch, HFA-305  
Food and Drug Administration  
5630 Fishers Lane, room 1061  
Rockville, MD 20852

**RE: Comments on Guidance for Industry entitled: ANDA's: Blend Uniformity Analysis**

Dear Sir/Madam:

This letter is in response to the Draft Guidance for Industry entitled "ANDA's: Blend Uniformity Analysis", which appeared in the August 3, 1999 issue of the *Federal Register*.

As a general comment, the agency is to be commended on the draft guidance. The guidance provides ANDA sponsors with a framework that defines the agency's position on blend uniformity requirements. Prior to the guidance, there was lack of consistency between reviewers, leading to numerous CMC deficiencies that could have otherwise been avoided. Overall, the draft guidance is excellent. The proposed requirements are realistic, not overly burdensome, and will provide ongoing assurance that drug products will meet uniformity requirements.

With respect to the provisions of the guidance, Purepac offers the following comments. Please note that these comments primarily address blends of dry solids. For other types of blends, the situation may differ.

99D-2635

C32

Sample Size:

- The draft guidance states that BUA samples be equal to, or in some circumstances, greater than one unit dose. It has been Purepac's experience that surface area effects can play a role in apparently non-uniform blend samples. In particular, multiple transfers of samples between the thief and the final laboratory testing solution can lead to erroneous results. Accordingly, we submit that a minimum sample size of 200 mg to 250 mg should be allowed as representative for dosage form weights below 200 mg. Smaller samples can greatly magnify the effect of contact surface areas in the sampling and during subsequent transfers.
- In addition, Purepac suggests that sponsors be allowed to sample less than a unit weight. There are situations where dose proportional strengths exist and are manufactured as separate batches (i.e. blends), and sampling of blend for all strengths in the same amount as the lowest strengths can simplify laboratory/method documentation and still provide adequate assurance that the blend is uniform.
- Finally, we note that larger sample sizes are contemplated in some circumstances, e.g. ten unit weights. This allowance infers that firms may engage in sub-sampling to obtain the quantity of sample intended for analysis. It has been Purepac's experience that sub-sampling of blends can distort results. Blend samples must be transported to the laboratory which can lead to changes in the blend, i.e. either segregation, or possibly improved uniformity. In addition, it is a common habit of chemists to "mix" any sample by inverting the container prior to sub-sampling. These situations raise the possibility that the portion (sub-sample) that is ultimately tested may not be representative of the material sent to the next phase of processing. We suggest that wherever possible, the entire blend sample be analyzed in one aliquot to avoid these potential issues.

#### Site of Sampling

- The draft guidance allows sampling from blending equipment or from drums. It has been Purepac's experience that segregation of blend components can occur when blends are discharged from blenders in some configurations. We would suggest that whenever possible, blend samples be taken from the same container that will be used to input the blend to the next (non-blending) manufacturing step. It has been Purepac's experience that sampling from drums is generally more fragile a procedure than sampling from blending equipment. However, the blend is not truly complete until any discharge step involved is completed. It is in sponsors' interest to be assured that blends are uniform before they are placed into the next step of the manufacturing sequence.
- We would suggest that wording be included to state that blend uniformity analysis is only required at the completion of mixing involved in a **final** blending operation. Where blending involves a pre-blend of fixed manufacturing instructions (equipment, quantities, times) which is then immediately further blended, blend uniformity should only be required at the completion of the final blending step.

#### Complex Manufacturing Procedures

- While we recognize that complex manufacturing procedures may require routine blend uniformity analysis, it should not be assumed that because a process appears complex, it automatically requires blend uniformity analysis. For example, a simple dry blend may be more prone to uniformity problems such as segregation than a wet slurry applied to sugar seeds in a rotogranulation process. In the case of the former, the blend components are simply a mixture of dry materials where as in the rotogranulation example, the components are firmly bonded to each sugar seed in an extremely well-mixed process. We would urge the agency to establish with reviewers that blend uniformity analysis is not required simply because a process appears complex.

RE: Comments on Guidance for Industry entitled: ANDA's: Blend Uniformity Analysis

Page 4 of 4

---

- Acceptance Criteria

The acceptance criteria defined in the guidance are appropriate for dosage forms that have a finished product assay specification of 90 – 100% of label claim. In cases where the finished dosage form has a tighter assay specification, the blend specification must be tightened accordingly. We recommend that the agency modify the guidance to accommodate these situations.

- Deletion of Blend Uniformity Analysis Requirement

The guidance, as written, appears to discourage the filing of supplements to request deletion of blend uniformity testing following ANDA approval. It is stated in the guidance that a blend uniformity test in an approved application is a means of satisfying the CGMP requirement at 21 CFR 211.110 (a)(3). We submit to the agency that the most effective (and mandated) means of demonstrating adequacy of mixing to ensure homogeneity is by properly validating the manufacturing process. Once the process has been validated and the firm has collected data on a number of batches demonstrating consistent and passing blend uniformity and finished content uniformity data, the agency should give due consideration to the firm's request to delete the blend uniformity test.

This concludes our comments on the proposed guidance regarding blend uniformity analysis. Should you have any questions or require further information, please contact the undersigned at (908) 659-2430.

Sincerely,

**PUREPAC PHARMACEUTICAL CO.**



Joan Janulis, R.A.C.

Vice President, Regulatory Affairs

cc: Douglas Sporn, OGD  
Dr. David Gill, OGD

Call 1-800-PICK-UPS (1-800-742-5877) or visit our Web site at [www.ups.com](http://www.ups.com)

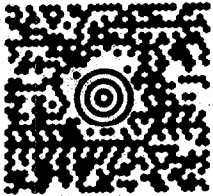
ir address label

eft of the address label.

or place parcel register tape above the address label.

1 OF 1

DEPARTMENT  
TICAL CO.



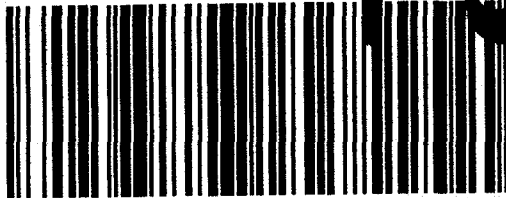
**MD 2070-10**



**UPS NEXT DAY AIR 1**

TRACKING #: 1Z 062 077 01 4711 10

ANAGEMENT BRANCH (HFA-305)  
RUG ADMINISTRATION  
S LANE, ROOM 1061  
E MD 20852



UOF 6.0.16 HP LaserJet 5Si/5Si MX PS 1024

Fold here and place in label pouch